Central fat and peripheral muscle: partners in crime in chronic obstructive pulmonary disease

Occasional Essay

Central Fat and Peripheral Muscle

Partners in Crime in Chronic Obstructive Pulmonary Disease

Bram van den Borst[1], Harry R. Gosker[1], and Annemie M. W. J. Schols[1]

[1]Department of Respiratory Medicine, NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University Medical Center+, Maastricht, The Netherlands

According to the World Health Organization, by the year 2020, chronic obstructive pulmonary disease (COPD) is expected to be the third-leading cause of death, and it is the only major chronic disease with an increasing mortality rate. Successful efforts to reduce this mortality will require a better understanding of the relationship between risk factors and the severity of the underlying lung disease. In patients with advanced disease, respiratory failure is the most common cause of death and weight loss and low muscle mass and strength are important determinants of mortality (1). In these patients, the risk of death is remarkably lower in obese patients. In contrast, in patients with mild-to-moderate disease, the primary cause of death is ischemic cardiovascular disease, for which overweight and obesity are important risk factors (2). The ongoing worldwide obesity epidemic necessitates an enhanced understanding of the interactions between cigarette smoke exposure, cardiovascular disease, skeletal muscle dysfunction, and adiposity in patients with COPD. In this essay, we discuss some of the mechanisms linking metabolism and adiposity with clinical outcomes in patients with COPD and offer tailored lifestyle interventions that may reduce morbidity and mortality in these patients.

DRIVERS OF CARDIOVASCULAR AND METABOLIC RISK IN COPD

Loss of Peripheral Skeletal Muscle Oxidative Phenotype

Muscle atrophy is highly prevalent in COPD irrespective of disease severity (3, 4). In moderate-to-severe COPD, this atrophy is associated with a reduction in the activity of oxidative enzymes, a decrease in mitochondrial density, impaired mitochondrial function, and a shift from fiber type I to type II (5). This loss of skeletal muscle "oxidative phenotype" has been associated with muscle fatigue (6) and decreased mechanical efficiency (7), and has also been demonstrated in patients with mild-to-moderate COPD in the absence of muscle atrophy (Figure 1) (8).

In diabetes, it has been proposed that skeletal muscle mitochondrial dysfunction may underlie peripheral insulin resistance via complex mechanisms including oxidative stress, intramuscular lipid accumulation, and inflammation (9, 10). However, tests of this hypothesis in human subjects have suggested that the mitochondrial defect observed in the skeletal muscles of patients with diabetes might be secondary to the insulin-resistant state instead of being a causal factor (reviewed in Reference 11). This notion is supported by striking parallels in skeletal muscle oxidative phenotype between underweight/normal weight nondiabetic patients with COPD and overweight/obese patients with diabetes. For example, decreased mitochondrial respiration has also been reported in patients with type 2 diabetes (12, 13), and the magnitude of reduced skeletal muscle peroxisome proliferator–activated receptor-γ coactivator-1α (PGC-1α) gene (the master regulator of mitochondrial biogenesis) expression is comparable between nonobese patients with COPD (8, 14) and obese subjects with type 2 diabetes (15). Also, several studies have shown evidence of a decreased type I fiber proportion in overweight/obese patients with type 2 diabetes compared with body mass index (BMI)-matched control subjects (16, 17). The decreased oxidative capacity of the skeletal muscle has been suggested to play a major role in "metabolic inflexibility" (18), which is defined by a reduced capacity to increase fat oxidation in response to increased fatty acid availability and an impaired switch from fat to glucose as the primary fuel source after a meal. Metabolic inflexibility may lead to the accumulation of intramyocellular lipids, which has been associated with insulin resistance through mechanisms possibly involving the lipid intermediates ceramides and diacylglycerol, which interfere with insulin signaling pathways (19). In the case of high caloric intake and lack of physical exercise, a positive energy balance may then further enhance ectopic fat deposition.

Investigators have employed homeostatic modeling of insulin resistance (homeostatic model assessment [HOMA] index) to show that insulin sensitivity is lower in nonobese and nondiabetic patients with COPD compared with BMI-matched healthy control subjects (20–22). The HOMA index, however, primarily reflects hepatic insulin sensitivity, whereas skeletal muscle insulin sensitivity can be most accurately assessed with the euglycemic insulin clamp technique. Therefore, clamp studies are indicated to prove or dispute that a decreased skeletal muscle oxidative phenotype is associated with insulin resistance at the level of skeletal muscle in COPD, as it is in diabetes.

Visceral Obesity

Several groups of investigators have suggested that low-grade systemic inflammation characteristic of a number of diseases, including COPD, is associated with an increased risk for the development of atherosclerosis and ischemic cardiovascular events (23). There is increasing evidence that adipose tissue is a significant contributor to the systemic inflammatory load in COPD. For example, a persistent systemic inflammation phenotype was described in patients with COPD and was associated with the BMI but not with the fat-free mass index, suggesting an inflammatory role for adipose tissue (24). Moreover, in a subgroup of patients with COPD, low-grade systemic inflammation has been positively related to total abdominal fat mass (25). Thus, adipose tissue dysfunction, including enhanced adipose tissue inflammation, may contribute to low-grade

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Correspondence and requests for reprints should be addressed to Annemie M. W. J. Schols, Ph.D., Department of Respiratory Medicine, NUTRIM School for Nutrition, Toxicology, and Metabolism, Maastricht University Medical Center+, P.O. Box 616, 6200 MD, Maastricht, The Netherlands. E-mail: a.schols@maastrichtuniversity.nl

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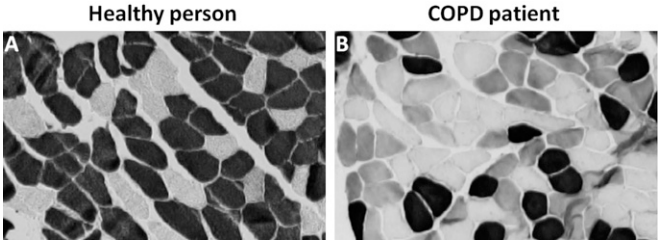

Figure 1. Peripheral muscle type I-to-II fiber shift, as an example of loss of oxidative phenotype in chronic obstructive pulmonary disease (COPD). Representative myosin heavy chain ATPase stainings of quadriceps muscle biopsies from (*A*) a healthy person and (*B*) a patient with COPD (FEV_1, 67% of predicted) matched for age, sex, and body mass index (25 kg/m^2). *Black fibers* indicate type I fibers and *dark* and *light gray fibers* correspond with type IIX and type IIA fibers, respectively. Pictures show representative photos from a previous study (8).

systemic inflammation in patients with COPD with absolute or relative fat abundance.

Abdominal visceral fat appears to be more strongly associated than subcutaneous fat with risk factors for cardiovascular and metabolic disorders, including hypertension and insulin resistance (26, 27), and is receiving increasing attention in COPD. Indeed, two studies have reported excessive visceral fat mass in nonobese patients with mild-to-moderate COPD as detected by computed tomography (CT) scanning (Figure 2) (28, 29). Moreover, excessive visceral fat mass was positively associated with circulating IL-6 levels, which were strongly associated with all-cause and cardiovascular disease mortality (28). Importantly, excessive visceral fat mass in these patients with COPD existed in the absence of obesity or increased abdominal circumference compared with the control persons in these studies, suggesting enhanced fat accumulation specifically in the visceral compartment. It is unclear whether the pulmonary impairment per se or an overall poor lifestyle, or both, predispose to excessive visceral fat accumulation. A similar selective increase in visceral fat mass has been observed in other chronic diseases characterized by tissue inflammation including rheumatoid arthritis, Crohn's disease, and psoriasis. These intriguing findings suggest a link between inflammation, visceral fat, and cardiovascular risk. Careful mechanistic studies will be required to determine whether an increase in visceral fat plays a causal role in this chain.

The inflammatory capacity of visceral fat is considerably greater than that of subcutaneous fat, and it has been suggested that visceral fat is an important source of IL-6 and IL-1β (30). In addition, there is evidence that an increase in visceral relative to subcutaneous fat is associated with hypertriglyceridemia and a decreased rate of glucose utilization in obese humans (31). Differential expression of the *fat mass and obesity associated* (*FTO*) gene has been associated with the differential deposition of fat in the visceral or subcutaneous stores, adipose tissue inflammation, and differences in the expression of inflammatory and insulin resistance–related genes in visceral compared with subcutaneous fat in otherwise healthy overweight/obese subjects (32). Consistent with the hypothesis that this gene may contribute to obesity-related inflammation in patients with COPD, single-nucleotide polymorphisms in the *FTO* gene were reported to be positively associated with BMI in patients with COPD (33).

Increased visceral fat mass has been associated with increased portal drainage of free fatty acids and adipokines to the liver, which may induce hepatic insulin resistance, inflammation, and oxidative stress ("portal hypothesis" [34]). Furthermore, visceral adiposity has been associated with fat deposition in other undesirable sites such as the liver, the heart, and the skeletal muscle (35). To date, there are no data available about whether ectopic fat deposition plays a role in the risk of cardiovascular and metabolic disease in COPD, but it may be involved in those with increased visceral fat mass.

There is increasing evidence that components of the metabolic syndrome are more prevalent in overweight patients with mild-to-moderate COPD compared with BMI-matched control subjects. A study reported that in overweight patients with COPD, 47% had the metabolic syndrome compared with 21% in BMI-matched

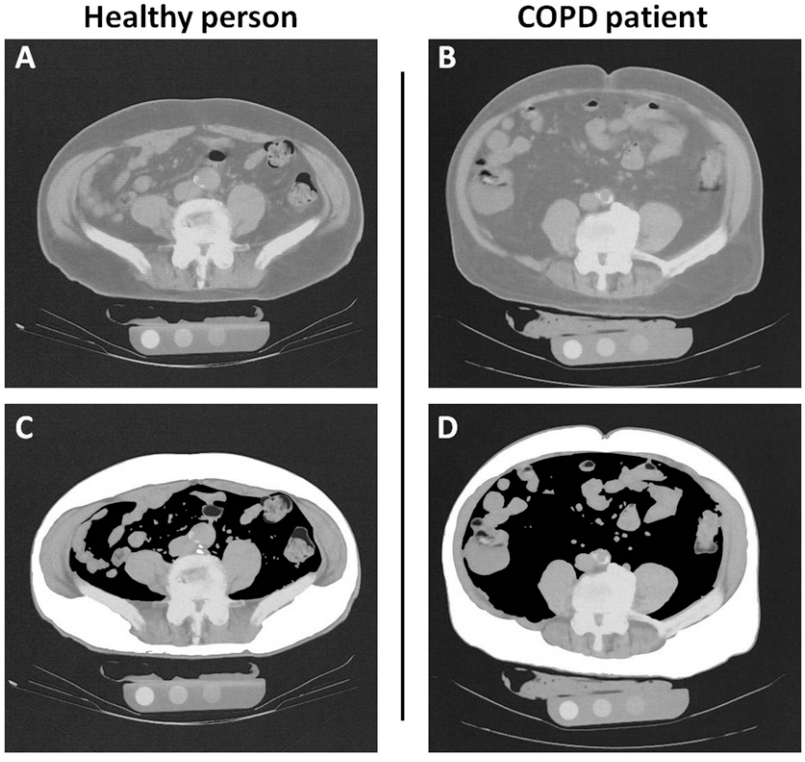

Figure 2. Excessive visceral fat accumulation but normal subcutaneous fat content in chronic obstructive pulmonary disease (COPD). Abdominal computed tomography (CT) scans from (*A*) a healthy person and (*B*) a patient with COPD (FEV_1, 53% of predicted) matched for age, sex, and body mass index (29 kg/m^2). The *black* and *white areas* in *C* and *D* denote the visceral and subcutaneous fat compartments, respectively. Pictures show representative CT scans from a previous study (28).

healthy subjects (36). In another study of 170 German patients with COPD, 53% of patients with moderate COPD (i.e., Global Initiative for Chronic Obstructive Lung Disease [GOLD] classification level II) met the criteria for metabolic syndrome and as much as 83% fulfilled the criteria for abdominal obesity (37). Congruently, a large population study showed that those with airflow obstruction had greater odds of having metabolic syndrome when adjusted for BMI, and when its components were further analyzed only abdominal obesity was significantly related to airflow obstruction (38).

LIFESTYLE INTERVENTION TO REDUCE THE RISK OF CARDIOVASCULAR AND METABOLIC DISEASE IN PATIENTS WITH COPD

Smoking Cessation

It is well known that smoking is an independent risk factor for both COPD and cardiovascular disease. Less recognized is that smokers have more central adiposity (39) and exposure to smoking is associated with poor skeletal muscle function (40). Data show that smokers are characterized by decreased skeletal muscle insulin sensitivity, which was partially reversible on smoking cessation. Experimental evidence suggests involvement of skeletal muscle mammalian target of rapamycin (mTOR) in this process, a crucial regulator of cellular protein synthesis (41). BMI, as well as whole-body muscle and fat masses, are comparably reduced in older patients with mild-to-moderate COPD and age-matched smokers without COPD compared with nonsmokers, suggesting a common insult earlier in life related to smoking (4). Furthermore, the peripheral skeletal muscle of smokers without COPD shows a loss of oxidative phenotype compared with nonsmoking healthy control subjects (42). Smoking induces low-grade systemic inflammation, independently of COPD (43), and the persistent systemic inflammation observed in patients with COPD was predicted by current smoking status (24). Notably, chronic exposure of mice to cigarette smoke also induces systemic inflammation and decreased skeletal muscle oxidative capacity (44). Smoking cessation is associated with fat mass gain, particularly in the visceral compartment (45), stressing the need for broad lifestyle interventions beyond smoking cessation.

Physical Activity and Aerobic Exercise Training

The Centers for Disease Control and Prevention and the American College of Sports Medicine recommend that a person should engage in at least 30 minutes of moderate-to-vigorous physical activity each day, preferably in bouts of 10 minutes or more (46). The majority of patients with COPD have a sedentary lifestyle (5) and physical inactivity contributes to the risk and mortality associated with cardiovascular and metabolic disease. Patients with COPD, irrespective of disease severity, have fewer, shorter, and less intense periods of intense physical activity, and spend more time at rest compared with healthy subjects (8). It has been argued that the reduced level of physical activity is causally implicated in the development of COPD, as studies have consistently reported attenuated FEV_1 decline in physically active persons (smokers and nonsmokers) (47).

Bed-rest studies in healthy, lean subjects have shown that physical inactivity induces a wide array of metabolic abnormalities including skeletal muscle insulin resistance, impaired skeletal muscle lipid trafficking, a shift in fuel metabolism in favor of carbohydrate oxidation and in detriment of lipid oxidation, an increase in intramyocellular lipid content, muscle atrophy and muscle fiber type I-to-II shift, and increased plasma nonesterified fatty acid levels (48). As many of these metabolic abnormalities have also been found in COPD, the adverse effects of physical inactivity are likely to be substantial.

The benefits of aerobic exercise training on cardiometabolic health have been well described in overweight or obese adults with and without type 2 diabetes, but have been incompletely studied in patients with COPD. In healthy overweight or obese adults, aerobic exercise training improves insulin sensitivity and induces mitochondrial biogenesis in the skeletal muscle (49, 50), and induces the loss of visceral fat mass (51). These effects were observed even in patients whose body mass or waist circumference did not change.

Classically, it was assumed that aerobic exercise training intensity in COPD could not reach the levels required to induce physiological effects because of ventilatory limitation. Two important papers disputed this assumption by showing improved lactate-to-work ratios and increased activity of key mitochondrial enzymes in muscle biopsies after aerobic exercise training (52, 53), and these findings have been subsequently confirmed.

Arterial stiffness is an independent cardiovascular risk factor, which is also improved by aerobic exercise training in healthy subjects (54). Increased arterial stiffness has been reported in patients with COPD, particularly those with advanced disease (55). Interestingly, Vivodtzev and colleagues reported that a relatively short aerobic exercise training program improved arterial stiffness and quadriceps muscle endurance in a cohort of patients with COPD (56). Gale and colleagues (57) showed that standard multidisciplinary pulmonary rehabilitation including aerobic exercise training reduced arterial stiffness without changing BMI in mildly overweight patients with COPD.

Diet and Nutritional Modulation

While weight gain and improved nutrition are recommended for underweight patients with COPD (58), there is no systematic study demonstrating efficacy of improved nutrition or weight reduction strategies in overweight or obese patients with COPD. It seems likely that the obesity paradox has limited enthusiasm for this approach. However, data from weight loss interventions in patients at risk for diabetes suggest that even modest reductions in weight can reduce the risk of cardiovascular and metabolic diseases, perhaps through improvements in body fat distribution. For example, an approximately 2–5% loss of body mass was reported to be associated with a sustained and preferential loss of visceral relative to subcutaneous fat in otherwise healthy overweight or obese persons; however, weight loss greater than 5% was associated with the loss of fat in both compartments (59).

Dietary factors have also been put forward as contributing environmental factors in COPD etiology and pathology. A diet rich in fruit, vegetables, whole-meal cereals, and fish is associated with a reduced COPD risk, whereas a "Western diet" rich in refined grains, cured and red meats, desserts, and French fries is associated with increased COPD risk, independent of smoking (60, 61). Further study is required to identify the specific dietary components with COPD risk as these strategies might be used to prevent the development or slow the progression of COPD while simultaneously reducing cardiovascular risk. The available literature suggests a particular important role for dietary fiber. There is convincing evidence of lower fiber intake in patients with COPD (28) and that increased dietary fiber intake is inversely associated with respiratory mortality (62). Dietary fiber has been shown to alter gut immunity and reduce systemic inflammation, which may be mediated by alterations in the gut microbiome or other mechanisms. Polyunsaturated fatty acids (PUFAs) warrant further investigation in targeted nutritional modulation as PUFAs (in particular n-3 fatty acids) are known agonists of peroxisome proliferator–activated receptors (PPARs), which are implicated in skeletal muscle oxidative gene expression. PUFA supplementation was also shown to enhance training effects on exercise capacity in a randomized controlled trial that included patients with moderate-to-severe COPD (63). PPARs as potential targets for nutritional as well

as pharmacological modulation in COPD have been discussed in detail elsewhere (64).

Another promising example of nutritional modulation to improve the cardiovascular and metabolic disease risk profile in COPD is resveratrol, a natural polyphenolic compound in nuts and grapes that is widely available as a nutritional supplement. Resveratrol supplementation (150 mg/d) has emerged as a calorie restriction mimetic with beneficial cardiovascular, antiaging, and antidiabetogenic properties in otherwise healthy overweight or obese men (65). Interestingly, pharmacological inhibition of phosphodiesterase-4 reproduced all of the metabolic benefits of resveratrol in experimental studies, likely through the same potential mechanisms. These include elevation of intracellular cAMP levels, thereby increasing NAD^+ and the activity of SirT1, which in concert provide a drive for increasing oxidative metabolism (66).

CONCLUSIONS

Adverse metabolic health, in terms of loss of peripheral skeletal muscle oxidative phenotype and excessive visceral fat accumulation, is associated with increased morbidity and mortality in patients with COPD. This increased risk is evident at all stages of the disease and is not necessarily restricted to obese patients. Ruderman and colleagues described this phenotype as a "metabolically obese, but normal weight person" (67). Physical inactivity, poor dietary quality, and smoking contribute to these metabolic abnormalities, and in concert further increase the risk of cardiovascular morbidity and mortality (Figure 3).

Because loss of muscle oxidative phenotype and excessive visceral fat accumulation can exist without changes in muscle mass and abdominal circumference, there is a need for new diagnostic tools and biomarkers to reveal these hidden phenomena. Quadriceps muscle endurance tests or the lactate response on exercise may provide good indicators of skeletal muscle oxidative phenotype, and abdominal bioelectrical impedance, ultrasound, and plasma levels of the prothrombotic adipokine plasminogen activator inhibitor-1 have shown good correlations with CT-acquired visceral fat mass but require validation in COPD.

The most important question that needs to be answered in future studies is whether the adverse metabolic profile in patients with COPD is caused by the disease itself or by an overall poor lifestyle, and whether the two act synergistically. Studies in patients with COPD and control subjects without COPD matched for overall lifestyle may help in disentangling COPD-specific versus lifestyle-mediated influences. Other important questions remain: Is the loss of peripheral skeletal muscle oxidative phenotype in COPD an accelerator of or causally implicated in insulin resistance? Is there a physiological link between the loss of peripheral skeletal muscle oxidative phenotype and visceral fat accumulation? Is the inflammatory status of visceral versus subcutaneous fat enhanced in COPD, and does this relate to an adverse cardiovascular or metabolic profile? What is the role of ectopic fat deposition in the adverse cardiovascular and metabolic profile in COPD? Finally, a possible link between adipose hormones and pulmonary inflammation may shed new light on the importance of adipose tissue in COPD progression in the current obesogenic society.

It is projected that increased knowledge of the metabolic changes in patients with COPD will allow investigators to test interventions aimed at reducing the risk of cardiovascular and metabolic diseases and their associated morbidity and mortality. Available data suggest that the early implementation of tailored lifestyle interventions in patients with COPD who are not yet physically impaired is likely to be beneficial. These lifestyle factors extend beyond recommendations for smoking cessation; instead, an integrated systems approach addressing smoking, physical inactivity, and poor diet may be most beneficial in slowing the progression of the disease.

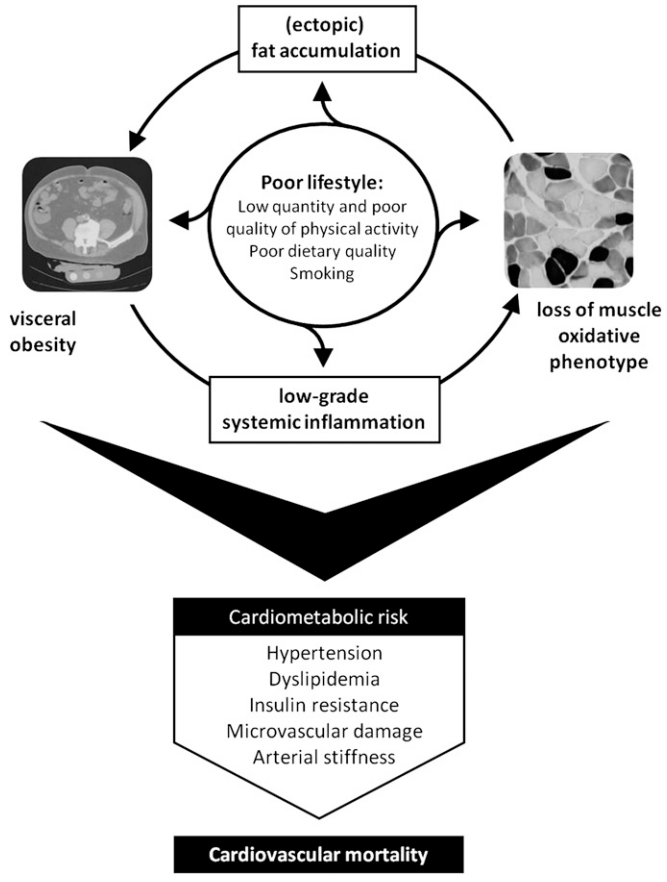

Figure 3. Conceptual representation of the drivers of cardiovascular and metabolic risk in chronic obstructive pulmonary disease (COPD).

Author disclosures are available with the text of this article at www.atsjournals.org.

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